REMARKS

Status of the Claims

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the specification, paragraphs have been amended on pages 30 and 34.

Claim 39 is currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

Upon entry of this Amendment, claims 38, 39, 41 and 57-59 will remain pending in the application.

Issues Regarding the Specification

The Examiner objects to the specification because of the following typographical errors:

A. Page 30, line 38 is missing an "α" after pSS.

B. Page 33, line 6 is missing a term in the parentheses before the term "ura")

With respect to (A), Applicants have amended page 30 line 38 as suggested by the Examiner. With respect to (B), Applicants note that the location in the specification for this amendment is page 34, line 6. Applicants have amended page 34, line 6 to recite the term "α" in the parentheses before the term "ura". Therefore, Applicants respectfully request withdrawal of the objection.

Applicants have also amended the specification to correct typographical errors. No new matter has been added.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 38, 39, 41 and 57-59 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner asserts that the specification allegedly fails to provide guidance of any signal sequence other than MFα1 and MFα1 with an STE13 mutation. The Examiner asserts that it would not be predictable to the artisan which signal sequence would be effective in the method. Applicants respectfully request reconsideration and withdrawal of the rejection.

The specification provides sufficient guidance for a person of ordinary skill in the art to use signal sequences other than MFα1 and MFα1 with an STE13 mutation. For example, a discussion of leader sequences useful in the claimed invention is provided in the specification on page 23, line 30, through page 26, line 8. A person of ordinary skill in the art, using the teachings of the present invention as well as techniques well known to those of skill in the art, would be able to construct a microorganism using a leader sequence selected from those disclosed in the specification or from leader sequences that were well known to those of skill in the art. Applicants remind the Examiner that Applicants are not limited by their enumerated examples. Therefore, the specification provides sufficient enablement for the claimed invention, and withdrawal of this ground for rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claim 39 is rejected by the Examiner under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner recommends amending claim 39 to replace the term "consisting of" with the term "comprising" because the term "consisting of" implies that PTH is the only substance in the medium, but the medium itself is considered another substance by the Examiner. Rather than replacing the term "consisting of" with the term "comprising", Applicants have amended claim 39 by replacing this term with the term "consisting essentially of." The term "consisting essentially of" is appropriate because the contents of the medium other than the PTH do not affect the basic and novel characteristics of the claim.

Issues Under Obviousness-Type Double Patenting

A. Claims 38, 39, 41 and 57-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 10 of U.S. Patent No. 5,420,242. Attached herewith as Exhibit 1 is a terminal disclaimer which disclaims the terminal part of the term of any patent granted on the above-identified application which would extend beyond the full statutory term, as presently shortened by any terminal disclaimer, of U.S. Patent No. 5,420,242. Therefore, this ground for rejection is moot.

B. Claims 38, 39, 41 and 57-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-38 of U.S. Patent No. 5,010,010. Attached herewith as Exhibit 2 is a terminal disclaimer which disclaims the terminal part of the term of any patent granted on the above-identified application which would extend beyond the full statutory term, as presently shortened by any terminal disclaimer, of U.S. Patent No. 5,010,010. Therefore, this ground for rejection is moot.

C. Claims 38, 39, 41 and 57-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1 and 2 of U.S. Patent No. 6,146,852. Attached herewith as Exhibit 3 is a terminal disclaimer which disclaims the terminal part of the term of any patent granted on the above-identified application which would extend beyond the full statutory term, as presently shortened by any terminal disclaimer, of U.S. Patent No. 6,146,852. Therefore, this ground for rejection is moot.

Claim Rejections - 35 U.S.C. § 102

Claims 38, 39, 41 and 57-59 are rejected by the Examiner under 35 U.S.C. § 102 as being allegedly anticipated by Breyel et al. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner states that it would be expected that before the cells of Breyel et al. are lysed, some PTH from the cells would have leaked into the medium making this fraction of

the medium cell free. Applicants respectfully disagree with the Examiner. Breyel does not teach that any PTH, intact or fragmented, leaked into the medium. The Examiner is only speculating and has failed to provide any scientific evidence showing that any PTH leaked into the medium from the cells of Breyel et al.

Furthermore, the cell-free medium of the present invention *is* distinct from the extract obtained by Breyel et al. The Examiner states that the extract of Breyel et al., which is obtained through sonication, is a cell free extract. The Examiner is correct. The extract of Breyel et al. is a cell free extract. However, a cell free extract containing PTH is not the same thing as the presently claimed cell free medium consisting essentially of PTH. A person of ordinary skill in the art would know this to be the case, as demonstrated by the attached excerpt from King and Stansfield, *A Dictionary of Genetics*, 1997, p53, Oxford University Press, New York (Exhibit 4) which includes a definition of the term cell-free extract:

> *[A] fluid obtained by rupturing cells and removing the particulate material, membranes, and remaining intact cells. The extract contains most of the soluble molecules of the cell...*

To obtain the extract of Breyel et al., PTH producing *E. coli* were lysed using sonication. The cell lysate was centrifuged and the supernatant containing PTH was collected. *See* Breyel et al. at page III-364. Thus, the extract of Breyel et al. contains most of the soluble molecules of the cell. In contrast, to obtain the cell free medium of the claimed invention, the cells are not lysed. Rather, the PTH is secreted into the medium by the microorganism. Therefore, the cell free medium of the claimed invention *only* contains compounds secreted by the microorganism.

Additionally, since Breyel et al. teaches a cell free extract and not a cell free medium consisting essentially of PTH, Breyel et al. fails to teach a manner of obtaining intact hPTH from a cell-free medium consisting essentially of PTH. Applicants note that page 366 of Breyel et al. indicates that the transient life for Breyel et al.'s PTH was minimal.

For the reasons discussed above, the present invention is not anticipated by the teachings of Breyel et al.

CONCLUSION

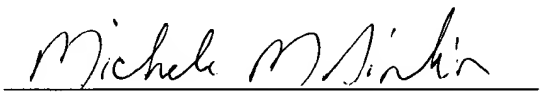
Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date December 31, 2003

By 

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

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In cell cultures the cells are not organized into tissues. *See* **Appendix C,** 1940. Earle: 1956. Puck *et al.*

cell cycle the sequence of events between one mitotic division and another in a eukaryotic cell. Mitosis (M phase) is followed by a growth (G_1) phase, then by DNA synthesis (S phase), then by another growth (G_2) phase, and finally by another mitosis. In HeLa cells (*q.v.*), for example, the G_1, S, G_2, and M phases take 8.2, 6.2, 4.6, and 0.6 hours, respectively. The period between mitoses ($G_1 + S + G_2$) is called interphase. Cells may have different doubling times, depending on their developmental stage or tissue type. The variation in doubling times is usually a function of the time spent in G_1. When a cell differentiates, it leaves the cycle and enters a phase designated G_0. Such "resting" cells are mitotically quiescent, but metabolically active. *See* **Appendix C,** 1953, Howard and Pelc; **check point, cyclins, MPF.**

cell determination an event in embryogenesis that specifies the developmental pathway that a cell will follow.

cell differentiation the process whereby descendants of a single cell achieve and maintain specializations of structure and function. Differentiation presumably is the result of differential transcriptions.

cell division the process (binary fission in prokaryotes, mitosis in eukaryotes) by which two daughter cells are produced from one parent cell. *See* **Appendix C,** 1875, Strasburger.

cell division cycle kinases *See* **cyclins.**

cell-driven viral transformation a method for creating immortalized human antibody-producing cells *in vitro* without forming a hybridoma (*q.v.*). Normal B lymphocytes from an immunized donor are mixed with other cells infected with the Epstein-Barr virus (*q.v.*). The virus enters the B lymphocytes. The cells originally infected with the virus are experimentally destroyed, and the virally transformed cells producing the antibody of interest are isolated. In cell-driven viral transformation, about 1 in 50 B lymphocytes is transformed, whereas with the cell hybridization technique only about 1 human cell in 10 million is transformed.

cell fractionation the separation of the various components of cells after homogenization of a tissue and differential centrifugation. Four fractions are generally obtained: (1) the nuclear fraction, (2) the mitochondrial fraction, (3) the microsomal fraction, and (4) the soluble fraction or cytosol. *See* **Appendix C,** 1946, Claude.

cell-free extract a fluid obtained by rupturing cells and removing the particulate material, membranes, and remaining intact cells. The extract contains most of the soluble molecules of the cell. The preparation of cell-free extracts in which proteins and nucleic acids are synthesized represent milestones in biochemical research. *See* **Appendix C,** 1955, Hoagland; 1961, Nirenberg and Matthaei; 1973, Roberts and Preston.

cell fusion the experimental formation of a single hybrid cell with nuclei and cytoplasm from different somatic cells. The cells that are fused may come from tissue cultures derived from different species. Such fusions are facilitated by the adsorption of certain viruses by the cells. *See* **polyethylene glycol, Sendai virus, Zimmermann cell fusion.**

cell hybridization the production of viable hybrid somatic cells following experimentally induced cell fusion (*q.v.*). In the case of interspecific hybrids, there is a selective elimination of chromosomes belonging to one species during subsequent mitoses. Eventually, cell lines can be produced containing a complete set of chromosomes from one species and a single chromosome from the other. By studying the new gene products synthesized by the hybrid cell line, genes residing in the single chromosome can be identified. *See* **Appendix C,** 1960, Barski *et al.,* **HAT medium, hybridoma, syntenic genes.**

cell interaction genes a term sometimes used to refer to some genes in the I region of the mouse H2 complex that influence the ability of various cellular components of the immune system to cooperate effectively in an immune response.

cell line a heterogeneous group of cells derived from a primary culture (*q.v.*) at the time of the first transfer. *See* **isologous cell line.**

cell lineage a pedigree of the cells produced from an ancestral cell by binary fission in prokaryotes or mitotic division in eukaryotes. *Caenorhabditis elegans* (*q.v.*) is the only multicellular eukaryote for which the complete pattern of cell divisions from single-celled zygote to mature adult has been elucidated. Cell lineage diagrams are available that detail each cell or nuclear division and the fate of each cell produced by a terminal division.

cell lineage mutants mutations that affect the division of cells or the fates of their progeny cells. Cell lineage mutants generally fall into two broad classes. The first contains mutations that affect general cellular processes, such as cell division or DNA replication. Mutants perturbing the cell division cycle have been analyzed most extensively in *Saccharomyces cerevisiae.* The second class of mutations shows a striking specificity in their effects.